REMARKS/ARGUMENTS

According to the Office Action, prior to the present amendment, claims 1-45 were pending in this application. Claims 31-45 were withdrawn from consideration, and claims 1-30 were rejected on various grounds. Claims 5, 8, and 11 were canceled by Applicant's amendment dated October 27, 2006, and should have been listed as such. The current submission includes the amendment of claims 1, 3, 6, 9, 10, 13-18, and 25, and the cancellation of additional claims 2, 7, 19-24 and 31-45. Thus, upon entry of the present amendment, claims 1-4, 6, 7, 9, 10, 12-18, and 24-30 are pending. Support for the recitation of "naturally occurring" variants is at least in paragraph [0025] of the specification as published (publication no. 20040146907). The other amendments are of formal nature. All amendments are fully supported by the specification as originally filed and do not add new matter. All amendments and cancellations were made without prejudice or disclaimer. Applicants explicitly reserve the right to pursue any deleted subject matter in one or more continuing applications.

Claim Rejections - 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-30 are rejected under 35 U.S.C. § 112, First Paragraph, as allegedly "failing to comply with the written description requirement."

The cancellation of claims 2, 5, 7, 8, 11 and 20-24 moots their rejection. The rejection of the remaining claims is respectfully traversed.

The rejection appears to be based on the finding that the specification does not provide adequate written description for variants of the individual genes specifically recited in the claims. In particular, the Examiner states that "in the context of measuring HGD by measuring gene expression, the specification fails to disclose a structural functional relationship between the claimed variants and their expression relative to the indication of HGD."

Without acquiescing to the rejection, or the reasoning underlying the rejection, claims 1, 6, 9, 13 and 25 have been amended to recite "naturally occurring" variants. This amendments is clearly supported by paragraph [0025] of the specification as published, which states: "Optionally, sequence variants are naturally occurring allelic variants, sequence variants or splice variants of these sequences." (Page 15, lines 9-10 of the specification as filed.) The specific sequences of SEQ ID NOS: 3, 13, 17, 23 and 43 are clearly representative of the narrow genera composed of these sequences and their respective naturally occurring variants, such as

allelic and splice variants, which can be readily identified using the sequences specifically disclosed. Accordingly, based on the disclosure provided in the specification, one of ordinary skill would reasonably accept that Applicant was in the possession of the invention at the time the application was filed, and the present rejection should be withdrawn.

Claim Rejection - 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-30 are rejected under 35 U.S.C. § 112, First Paragraph, as allegedly "failing to comply with the enablement requirement."

The cancellation of claims 2, 5, 7, 8, 11 and 20-24 moots their rejection. The rejection of the remaining claims is respectfully traversed.

The Examiner's arguments in support for the rejection

The Examiner notes: (1) "[t]he claim breadth is broad since it is directed to a method of detecting all types of high grade dysplasia regardless of its tissue origin by monitoring the expression of the recited 5 genes in any type of mammal"; (2) [t]he specification fails to disclose whether elevated expression of the combination of said genes is indicative of *any* type of dysplasia in *any* type of mammal." (Passage bridging pages 4 and 5 of the Office Action, emphasis added.)

In support of these statements, in order to illustrate the state of the art and the alleged unpredictability in the art, the Examiner cites **Shalon et al.** (US 2001/0051344) as allegedly teaching "that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant." Shalon et al. is further relied on for teaching that "at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data," and that at least 2 fold and up to 100 fold or more increase or decrease in gene expression levels relative to control levels is considered significant. (Passage bridging pages 5 and 6 of the Office Action.)

Kroese et al. is cited for its teaching of issues related to the validity and predictive value of genetic testing, including that (1) "genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be rightly defined," (2) "a particular genetic test to be evaluated may be caused by more than one gene and these variations

may be due to deletions and insertions not detected by routine sequence methods," (3) "genetic test is shorthand to describe a test to detect a particular genetic variants for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes," and (4) all measures of the test performance should be presented with their 95% confidence intervals (Passage bridging pages 5 and 6 of the Office Action, citing page 476, 2nd column, last paragraph and page 477, 1st column, 1st full paragraph of the paper.)

Lucenti is cited for its alleged teaching that "it is strikingly common for follow-up studies to find gene-disease associations wrong," and "typically when a finding is first published linking a given gene to complex disease there is roughly a one-third chance that the study will reliably confirm the finding." (Page 6 of the Office Action.)

The Examiner further notes that in the present case, "the issue is complicated by the fact that the claims encompass genes of various function and are involved in different diseases," and thus, "the recited genes may have elevated expression due to different causes than that is correlated with high grade dysplasia." Finally, the Examiner adds, without any evidence: "whether the elevated expression of the claimed genes in intestinal metaplasia and esophageal dysplasia can extend the predictability to dysplasia of other tissue origin is unpredictable."

The Examiner concludes that, in view of the alleged unpredictability in the art and the limited teaching in the specification, undue experimentation would be needed to practice the invention within the full scope of claims, and therefore, the claims are not enabled.

The invention as claimed is enabled

(i) *The invention claimed*

According to the rejection, the claims are "directed to a method of detecting all types of high grade dysplasia regardless of its tissue origin by monitoring the expression of the recited 5 genes in any type of mammal." This statement is factually incorrect. Even before the present amendments, all independent claims (claims 1, 6 and 9) recited that the gene expression levels were determined in a tissue from esophagus or colon. Accordingly, the claims were not directed to a method measuring gene expression levels regardless of tissue origin. Furthermore, the

claims have not been amended to recite human tissue and cells of human tissue, thus they are not directed to monitoring gene expression in "any type of mammal."

For similar reasons, the Examiner's question "whether the elevated expression of the claimed genes in intestinal metaplasia and esophaneal dysplasia" can be extended to "dysplasa of other tissue origin" is misplaced. As elevated expression of the genes in the intestines and esophagus has been demonstrated, and detection of expression levels in other types of tissue is not claimed, it is irrelevant for assessing enablement for the pending claims whether the disclosed experimental data could be extrapolated for expression levels in other types of tissues.

(ii) *State of the art and alleged unpredictability in the art*

Starting with **Kroese et al.**, the paper addresses certain issues concerning the evaluation and validation of genetic tests. As noted on page 475, 2nd column: "A genetic test has been defined as the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect *heritable disease related* genotypes, mutations, phenotypes, or karyotypes for clinical purposes." (Emphasis added.) While the authors focus on the analysis of human DNA, their review still remains within the general framework of genetic testing, focusing on *inheritable, genetic disorders*. This is clear from the listing of the various applications of genetic tests on page 476, 2nd column, including:

> "(1) Diagnostic testing to confirm or rule out a known or suspected *genetic disorder* in a symptomatic individual; (2) Predictive testing to determine the probability of asymptomatic individuals who are suspected of having an *inherited disorder* developing the clinical manifestations; (3) Susceptibility (or predisposition) testing to determine the risk or probability that individuals with the *genetic mutation* will develop a particular disease; (4) Carrier testing to identify individuals who have a *gene mutation* for a disorder *inherited in an autosomal recessive or X-linker recessive manner*; (5) Prenatal testing to determine during pregnancy whether there is an increased risk of having a child with a *genetic condition*; and (6) Population screening to identify asymptomatic individuals from within a particular community or a subsection of that community who have an increased change of having a specific *genetic disorder*, or carrying a specific *genetic predisposition to disease*, or of being a carrier of a *recessive genetic variant.*

Thus, all of Kroese's remarks, concerns and conclusions relate to genetic tests of inheritable diseases and conditions based on the testing of gene mutations, or, more specifically,

drawing conclusions from a finding that the test indeed detects the specific mutation or mutations that it was intended to detect, and does not detect specific mutation or mutations that are not present (see, e.g. the passage bridging pages 475 and 476). Since the invention claimed in the present application is not a "genetic test" and is not directed to the detection of inheritable gene mutations or gene mutations of any kind, Kroese's comments on the heterogeneous nature of genetic conditions, the complexities of genetic tests, and other conclusions do not apply.

Lucentini's provocative statement that gene association studies are typically wrong also concerns studies identifying diseases based on genetic mutations, thus has no bearing on the studies disclosed and the invention claimed in the present application.

This leaves us with **Shalon et al.** (US 2001/0051344), which was cited for allegedly teaching that at least 5 and preferably 20-50 different tests individuals should be assayed to obtain statistically meaningful data, and that typically at least 2 fold increase or decrease in gene expression level on a microarray is required relative to control. First of all, Shalon et al. does not properly represent the state of the art at the time the present invention was made, since it claims 1994 and 1995 priority dates, which are 8 or 7 years before the priority date of the present application. In a rapidly advancing field as gene expression profiling, 7 or 8 years make an enormous difference in the overall level of knowledge, and statements and conclusions made in 1994 do not necessarily apply in 2002. Indeed, the question whether a certain fold increase is statistically significant, is also a function of the sensitivity of the technique and equipment used for gene expression profiling. Thus, Shalon et al.'s statement that a statistically significant difference in gene expression levels is typically at least 2 fold, does not mean that 1.5 fold difference cannot be viewed, as recited in the present claims, cannot be viewed as statistically significant. This is further supported by the use of the qualifier "typically" which means that the two fold difference is not a strict requirement. As far as the suggestion that at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data (paragraph [0156]), the test disclosed in the present application fully meet this standard. As discussed on page 86 of the specification, the samples analyzed included samples of BE altogether from 27 patients, and samples of dysplasia from 8 patients.

In conclusion, the cited references are either not relevant to the invention claimed in the present application or do not supply information that would establish that the claimed invention does not reasonably follow from the experimental data on which it is based.

(iii) *The teaching provided in the specification*

As discussed above, the specification discloses experimental data performed with a variety of tissue samples obtained from a plurality of patients. As discussed in Example 3, the experimental results were subjected to rigorous analysis, including calculation of standard deviation and normalization. As discussed in Example 4, genes with elevated expression were identified as those with Z scores of >1.7 ($p<0.05$) in the disease group, corresponding to ration values of 2-20 in most cases. The genes listed in the present claims satisfied these criteria.

In conclusion, the invention claimed in the present application is reasonably based on the teaching of the specification and general knowledge in the art at the priority date of the present application. Accordingly, the invention can be practiced within the full scope of claims pending without undue experimentation, and the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. 112, Second Paragraph

Claims 3, 10, and 14-27 were rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite.

Claim 3 was rejected since it was deemed unclear whether it referred to "a method according to claim 1" or to "a test tissue sample according to claim 1." The current amendment makes it clear that claim 3 recites a method according to claim 1.

Claim 10 was found indefinite its is recitation of "at least eight polypeptides" which had no antecedent basis. The claim has been amended to recite "five polypeptides" which is believed to obviate this rejection.

Claims 14-24 were rejected for their recitation of "at least eight/ten/twelve/fifteen . . . genes," which was without antecedent basis in claim 13. Claims 19-24 have been canceled, and claims 14-18 have been amended by deleting the reference to the number of genes. Accordingly, the present rejection is moot.

Claim 25 has been rejected for its recitation of "a probe comprising at least 50 contiguous nucleotide from a gene selected from the group to nucleic acid of cells of test tissue sample relative to cells of normal tissue control." The current amendment of claim 25 is believed to obviate this rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including fees for extension of time, and credit overpayments to Deposit Account No. **08-1641** (**Attorney's Docket No. 39766-0235R1 US**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully Submitted,

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